PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Masao SUDOH, *et al.*

Docket No: Q94121

Appln. No.: 10/574,477

Group Art Unit: 1621

Confirmation No.: 2361

Examiner: Sudhakar KATAKAM

Filed: January 9, 2007

For: DRUG CONTAINING (2R)-2-PROPYLOCTANOIC ACID AS THE ACTIVE INGREDIENT

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Seiichi TANIKAWA, hereby declare and state:

THAT I am a citizen of Japan;

THAT I have received the degree of a Master of Pharmaceutical Science in 1995 from Kyoto University;

THAT I have been employed by Ono Pharmaceutical Co., Ltd. since 1995, where I have engaged in research of infusion preparation;

THAT this declaration is made in support of the above-identified U.S. Patent Application;

THAT I am a co-inventor of the present application;

THAT the following experiment was conducted by me.

Experiment

According to methods in Example 15 and Example 16 of the present application, disodium hydrogen phosphate·dodecahydrate (8.0 kg) and (2R)-2-propyloctanoic acid (5.0 kg) were added to water for injection, and an appropriate amount of sodium hydroxide was added thereto to adjust the pH of the mixture to 8.4 to 9.0. Water for injection was further added thereto to give a total volume of 100 L. The mixture was made to a homogeneous solution

and then filtered on a sterilizing filter (Durapore 0.22 μm membrane), and the resulting solution was charged with molding (blow fill sealing) into plastic ampoules. These ampoules were autoclaved (123°C, 15 min), and thus the medicaments of the present invention which comprises (2R)-2-propyloctanoic acid in concentration of 50 mg/mL was obtained.

According to the following method, changes of compounding were investigated when (1) physiological saline solution, (2) 10% concentrated glycerol and 5% fructose injection solution, (3) injection solution of dextran 40, (4) 10% injection solution of maltose or (5) physiological saline solution comprising ozagrel sodium (20 mg) was used as dilution liquid for the medicament and infusion was prepared.

Thus, 10 mL, 2 mL or 0.2 mL of the medicament (50 mg/mL) prepared in Example 15 or 16 was diluted with injection solution of the above (1) to (5) to make the total amount 100 mL (5 mg/mL, 1 mg/mL or 0.1 mg/mL). The appearances immediately thereafter and after 4 and 24 hours were observed by naked eye. Additionally, pH of the mixed solution and remaining ratio of (2R)-2-propyloctanoic acid in the mixed solution was measured. As a control, a preparation where (2R)-2-propyloctanoic acid was directly added to the injection solution was used.

< Result >
The medicament (Ex 15 or 16) prepared in Example 15 or 16 did not show clouding upon dilution with injection solution for production of injeciton; and the injeciton was colorless and clear and has pH value close to neutral which can be administered to living body even after 4 or 24 hours from preparation. Additionally, remaining ratio of (2R)-2-propyloctanoic acid at completion of each test is 95% or more. On the contrary, in the control, clouding was observed in the case of any of the infusion solution and was considered to be inappropriate to be administered to a living body. Additionally, when a similar experiment was carried out with a medicament which was prepared by using only (2R)-2-propyloctanoic acid and sodium hydroxide, clouding was observed and considered to be inappropriate to be administered to a living body.

As shown from the above result, medicament of the present invention is a medicament which has the following remarkable features: (2R)-2-propyloctanoic acid which is insoluble in water can be dissolved in water in high concentration in the medicament; the medicament of the present invention has resistance to pH fluctuations using solution and/or dilution liquid before use ; and it is possible to prepare infusion which has pH which can be administered to patients without clouding.

Name of injection solution	Time (after)	5 mg/mL		1 mg/mL		0.1 mg/mL	
		Ex 15 or 16	Control	Ex 15 or 16	Control	Ex 15 or 16	Control
Physiological saline solution	0 hour	Colorless and clear (pH 8.0)	Clouding or precipitation	Colorless and clear (pH 7.8)	Clouding or precipitation	Colorless and clear (pH 7.4)	Clouding or precipitation
	4 hours	Colorless and clear (pH 8.0)	Clouding or precipitation	Colorless and clear (pH 7.9)	Clouding or precipitation	Colorless and clear (pH 7.2)	Clouding or precipitation
	24 hours	Colorless and clear (pH 8.0)	Clouding or precipitation	Colorless and clear (pH 7.8)	Clouding or precipitation	Colorless and clear (pH 7.2)	Clouding or precipitation
10% Conc. glycerol + 5% fructose injection	0 hour	Colorless and clear (pH 7.8)	Clouding or precipitation	Colorless and clear (pH 7.5)	Clouding or precipitation	Colorless and clear (pH 6.2)	Clouding or precipitation
	4 hours	Colorless and clear (pH 7.8)	Clouding or precipitation	Colorless and clear (pH 7.4)	Clouding or precipitation	Colorless and clear (pH 6.2)	Clouding or precipitation
	24 hours	Colorless and clear (pH 7.8)	Clouding or precipitation	Colorless and clear (pH 7.4)	Clouding or precipitation	Colorless and clear (pH 6.2)	Clouding or precipitation
Dextran 40 injection	0 hour	Test was not carried out.		Colorless and clear (pH 7.5)	Clouding or precipitation	Colorless and clear (pH 6.3)	Clouding or precipitation
	4 hours			Colorless and clear (pH 7.5)	Clouding or precipitation	Colorless and clear (pH 6.3)	Clouding or precipitation
	24 hours			Colorless and clear (pH 7.5)	Clouding or precipitation	Colorless and clear (pH 6.3)	Clouding or precipitation
10% Maltose injection	0 hour	Test was not carried out.		Colorless and clear (pH 8.1)	Clouding or precipitation	Colorless and clear (pH 7.6)	Clouding or precipitation
	4 hours			Colorless and clear (pH 8.1)	Clouding or precipitation	Colorless and clear (pH 7.6)	Clouding or precipitation
	24 hours			Colorless and clear (pH 8.0)	Clouding or precipitation	Colorless and clear (pH 7.5)	Clouding or precipitation
Ozagrel sodium (20 mg in saline solution)	0 hour	Colorless and clear (pH 8.0)	Clouding or precipitation	Colorless and clear (pH 7.8)	Clouding or precipitation	Colorless and clear (pH 7.6)	Clouding or precipitation
	4 hours	Colorless and clear (pH 8.0)	Clouding or precipitation	Colorless and clear (pH 7.8)	Clouding or precipitation	Colorless and clear (pH 7.6)	Clouding or precipitation
	24 hours	Colorless and clear (pH 8.0)	Clouding or precipitation	Colorless and clear (pH 7.8)	Clouding or precipitation	Colorless and clear (pH 7.5)	Clouding or precipitation

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11/18/2010

Seiichi Tanikawa

Seiichi TANIKAWA